

U.S. Appln. Ser. No.: 09/410,484

Attorney Docket No. NATNUT-03972

In re Application of: Jan Wadstein *et al.*

Serial No.: 09/410,484

Group No.: 1614

Filed: 09/30/99

Examiner: Webman

Entitled: **Method Of Treating Hypertension And Reducing Serum Lipase Activity**

Declaration of Dr. Inge Bruheim

EFS WEB-FILED

Assistant Commissioner for Patents

Washington, D.C. 20231

I, Dr. Inge Bruheim, state as follows:

1. My present position is Senior Research Scientist, Aker Biomarine AS, the current owner of the instant patent application. I have a Ph.D. in Chemistry from the University of Oslo (Norway) and more than 4 years of industry experience in chemical research.

2. The Examiner states on page 3 of the Office Action that Shinitzky et al. teaches that linoleic acid (C18:2, cis-9,cis-12) can be used to treat hypertension. One of skill in the art would not interpret Shinitzky as providing this teaching. The Examiner specifically refers to Claims 1, 4, and 24 of Shinitzky as providing the teaching that linoleic acid can be used to treat hypertension. What those claims teach is that hypertension can be treated by administering a complex mixture comprising “a lipid fraction derived from natural sources (AL), said lipid fraction containing 40-80 weight percent glycerides, 3-5 weight percent cholesterol, 10-30 weight percent lecithin (phosphatidyl choline), 5-15 weight percent phosphatidyl ethanolamine and 2-5 weight percent negatively charged phospholipids, wherein the ratio of unsaturated to saturated fatty acids is at least 1:1” (Claim 1) and that the fatty acid component of this complex mixture comprises “Palmitic acid 35-45%, oleic acid 35-45%, linoleic acid 5-10%, stearic acid 5-7%, palmitoleic acid 2-3%, arachidonic acid 0.2-1%” (Claim 4). Shinitzky et al. does not teach that linoleic acid can be used to treat hypertension or that among all of the components of the

complex mixture, linoleic acid is sufficient to treat hypertension. Shinitzky et al. teaches that complex lipid fraction can be used to treat hypertension. This is not the same as teaching that linoleic acid can be used to treat hypertension. Indeed, one of skill in the art would recognize that any of the other components could be responsible for the hypertensive effect or that a combination of the components is necessary.

3. The Examiner further states the positional and geometric isomers of linoleic acid would be expected to have similar properties to linoleic acid in the absence of evidence to the contrary. Isomers of conjugated linoleic acid have different biological properties than linoleic acid. This was known in the art prior to the filing date of this application and has been substantiated in many publications after the filing date of this application. I have included several references, which are attached, that establish that the conjugated isomers of linoleic acid have distinct biological properties as compared to standard linoleic c9,c12 linoleic acid. Many of these references utilize corn oil, which comprises c9,c12 linoleic acid, as a control. All of the references show that the conjugated linoleic acid isomers have distinct biological properties. Furthermore, Dr. Mark Cook, the inventor of the cited 5,554,646 patent, is an author on most of these publications.

Yang M, Cook ME. Dietary conjugated linoleic acid decreased cachexia, macrophage tumor necrosis factor- α production, and modifies splenocyte cytokines production. *Exp Biol Med* (Maywood). 2003 Jan;228(1):51-8.

Li G, Dong B, Butz DE, Park Y, Pariza MW, Cook ME. NF- κ B independent inhibition of lipopolysaccharide-induced cyclooxygenase by a conjugated linoleic acid cognate, conjugated nonadecadienoic acid. *Biochim Biophys Acta*. 2006 Sep;1761(9):969-72.

Park Y, Storkson JM, Liu W, Albright KJ, Cook ME, Pariza MW. Structure-activity relationship of conjugated linoleic acid and its cognates in inhibiting heparin-releasable lipoprotein lipase and glycerol release from fully differentiated 3T3-L1 adipocytes. *J Nutr Biochem*. 2004 Sep;15(9):561-8.

Park Y, Storkson JM, Ntambi JM, Cook ME, Sih CJ, Pariza MW. Inhibition of hepatic stearoyl-CoA desaturase activity by trans-10, cis-12 conjugated linoleic acid and its derivatives. *Biochim Biophys Acta*. 2000 Jul 19;1486(2-3):285-92.

Park Y, Albright KJ, Liu W, Storkson JM, Cook ME, Pariza MW. Effect of conjugated linoleic

acid on body composition in mice. *Lipids*. 1997 Aug;32(8):853-8.

Chin SF, Storkson JM, Albright KJ, Cook ME, Pariza MW. Conjugated linoleic acid is a growth factor for rats as shown by enhanced weight gain and improved feed efficiency. *J Nutr*. 1994 Dec;124(12):2344-9.

Miller CC, Park Y, Pariza MW, Cook ME. Feeding conjugated linoleic acid to animals partially overcomes catabolic responses due to endotoxin injection. *Biochem Biophys Res Commun*. 1994 Feb 15;198(3):1107-12.

4. I further declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Dr. Inge Bruheim

Date: 23/10 - 2007